FDA Inspections Guide

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WHY IS THIS HAPPENING?

During the conduct of a clinical trial, Principal Investigators must:

- ✓ ensure that an investigation is conducted according to the investigational plan, protocol and regulations
- ✓ protect the rights, safety, and welfare of study participants
- ✓ obtain IRB approval prior to executing study procedures
- ✓ appropriately obtain Informed Consent from study participants
- ✓ control the drugs and devices under investigation

The FDA evaluates clinical trials to ensure compliance with Good Clinical Practices (GCP) and Federal regulations. They ensure that the rights, safety, and welfare of human subjects were protected, and the safety and efficacy of the data submitted in marketing applications.

FDA inspections can be either:

- Routine or Surveillance: those studies under pre-marketing application review
- For Cause or Directed: based on a potential regulatory violation and/or related to a complaint

TIMELINE OF FDA INSPECTIONS

Pre-Announcement: This can be up to 5 days before the start of the inspection. Communication would include details like the scope and logistics.

Opening Meeting/Interview: This will include the presentation of the FDA Form 482 "Notice of Inspection" and presentation of the Inspector's credentials. It should involve the Principal Investigator (PI) and any key study personnel and Institutional Officials. The topics of discussion would be:

- The number of studies or a list of the studies conducted the PI
- An overview of the study
- Facility tour
- The number of study participants
- The study data to be reviewed including deviations and SAEs
- The availability of the PI and key personnel for meetings or questions
- The best process to provide or obtain copies of study materials

Review of Study and Participant Records:

See additional details under **What to expect**

Close-Out Meeting:

This will include the summary of the Inspectors' findings and if applicable, the presentation of the Form 483 which details the observation of deviation from federal regulations.

PI Response:

- Verbal (at the Close-Out Meeting)
- Written (within 15 days of the Inspection)
    - Corrective Action Plan (CAPA)

Final FDA Classification:

- No Action Indicated (NAI)
- Voluntary Action Indicated (VAI)
- Official Action Indicated (OAI)
    - Warning Letter
    - Investigator not able to conduct clinical investigations involving products regulated by the FDA
- Other Actions:
    - Debarment
    - Civil Money Penalties

WHAT TO EXPECT

The FDA Inspection will focus on the following:

- **Was the study conducted according to the protocol?**
    - Data Collection
    - Inclusion Criteria and Exclusion Criteria
    - Randomization and Blinding/Unblinding Procedures
    - Study Visits, Study Procedures, Study Assessments & Evaluations
    - Study Drug Administration
- **Did the study comply with regulations?**
    - IRB Approvals
    - Informed Consent Process
    - Adverse Event Reporting
    - Study Drug Accountability
    - Records Management e.g. electronic
    - Financial Disclosures

The FDA Inspection will perform source data verification. The Inspectors will compare the original data collected and documented by the study site with the study data submitted to the FDA.

- Primary Endpoints
- Adverse Events
- Protocol Deviations
- Laboratory Data

The FDA Inspector will review the following study records:

Protocol	IRB correspondence/communications *e.g. submissions & approvals*
Sponsor Correspondence	Sponsor Monitoring Reports
Form FDA 1572 *Note that the DOA Log and CVs (qualifications) are reconciled against this in some cases*	Financial Disclosure Forms
Training Logs	Delegation of Authority Log
Laboratory Certifications	Investigational Product / Device Accountability Records
Informed Consent Forms	Adverse Event Reports
Source Documents	Progress Notes
Adverse Event Reports	Laboratory / Specimen Records *e.g. accreditation local & central*

HOW TO PREPARE

Planning

- Reserve a private, quiet area (e.g. office; conference room, etc.)
    - Prepare for Inspector to be present for two (2) or more days.
- Notify any other applicable parties of the FDA Audit scheduled
- Identify a point person who will assist and oversee the inspection
    - The FDA inspector must be accompanied at all times
- Upon the FDA Inspector's arrival, make sure you ask to see their credentials/identification prior to allowing them access to your study records
- PI to sign the FDA Form 482 "Notice of Inspection"
- Provide the Inspector only with files that have been requested
- Make copies of any documents that are requested by the Inspector

Preparation of Study Materials

1. Your study materials must be in as much order as they can be.
2. **Do not correct, amend, or revise any study document unless absolutely necessary.**
    a. The best practice is to document in a narrative notation: What was done, why it was done, when it was done, how it was done, what was the outcome, and who did it. If there is conflicting documentation or discrepancies in source documents, clarification is required.
    b. Notate corrected, amended, or revised items by crossing out and/or marking as "Late Entry" (as applicable) and list the date of the change and the initials or signature of the person making the change.
3. Create Notes to File to explain any discrepancies, missing items, etc. that are noted.
4. Read and review the corrective actions for all deviations. Familiarize yourselves with all justifications and rationales. Be prepared to verbalize steps taken to help avoid future occurrence.

5. Locate items not to be included in the Regulatory Binder that are maintained elsewhere, such as identifiable patient information, agreements, contracts, budgets, W-9s, participant compensation, etc.
6. Make sure the Delegation Log has the appropriate end dates for all staff no longer employed in the department and make sure it is up-to date with any applicable new research staff from study start to present.
7. Print all key essential regulatory documents found in Complion (e.g. protocols that were applicable when the study was active; blank ICFs that were applicable when the study was active, etc.)
8. Place either directional Notes to File (NTF) in the paper-based Regulatory Binder regarding if essential documents can be found in Complion or NTFs explaining why sections are empty/blank.
9. NTF are needed for the location of all financial info since they are kept separate but can be made available upon request.
10. As applicable, draft a Note to File explaining that the applicable external lab CLIA, CAP certificates, Lab Director CV and lab reference ranges can be made available upon request. Note that you should obtain these prior to any audit and have them available upon request.
11. Please file, staple or hole-punch any loose files that are in the pocket of any binder, so they are secure and will not, in error, fall out and become difficult to attribute to a specific binder.
12. Remove sticky notes from the source binders if not original source. If original source, staple them on the page. Also, address any comments or issue noted.
13. Prepare a list of all FDA regulated studies for the Principal Investigator (active or closed). This list should include protocol title, start, and stop dates
14. Create a list of site-specific UH SPARTAIRB Reportable New Information (RNIs).
15. Create a list of site-specific Protocol Deviations. *Reference the template that can be found here.*
16. Create a list of site-specific Adverse Events. *Reference the template that can be found here.*
17. Create a list of all Internal and External Safety Reports related to the Investigational Product(s)/Device(s) (SUSAR/MedWatch, etc.). *Reference the template that can be found here.*
18. Provide copies of PI CV, medical license, and HRP/CITI/GCP certificate to external auditors only upon request.
19. Multiple options are available to securely and confidentially provide the source data:
    - **Option 1**: Provide certified copies of the electronic study records. See SOP SC-410 - Certified Copies of Research Regulatory Documents for details.
    - **Option 2**: Screen share via Zoom teleconference. Key staff navigate through the information only.
    - **Option 3**: Screen share on a projector in a conference room or office. Key Staff navigate through the information only.
    - **Option 4**: Screen share the content on a PC/Laptop in a conference room or office. Key staff navigate through the information only.
    - **Option 5**: Send study data securely and encrypted via an UH email. See Job Aid: Sending and Viewing Encrypted UH Email for details.
    - **Option 6**: Obtain a USB from a Clinical Research Center representative to share only relevant and pertinent study data.
        - Provide copies of the electronic study data on a UH-approved encrypted USB device, but they cannot take this with them e.g., the Inspector must return it at the end of the audit. If they want to take something with them it should be their own copies that you have confirmed, you have a copy of them too and you know for what purposes they are keeping it.

HOW TO COMPLETE THE INSPECTION

- Document all of your interactions and communications with the FDA: names; titles; dates; a summary of the conversations; and retain copies of what was provided if asked e.g. essential documents.
- Set aside time each day to speak with the Inspector and be available for any questions that may arise each day.
    - If unable to be present the entire time, delegate a trusted, individual who is knowledgeable about the trial and one who will keep information private and confidential. They should be guided to compile questions and pose those directly to the PI once they return or are available, especially if they cannot honestly answer with accuracy and completeness.
- Only answer specifically to any questions that are asked.
- Be upfront, truthful, and transparent.
- Stick to the facts and what can be confirmed.
- If you are unclear of any question, ask them to repeat or rephrase the question and if you just don't know, please just tell them that.
- If any deficiencies are noted at the conclusion of the FDA audit (*on the FDA Form 483*) before you complete this, consult with either the UH IRB, UH Legal Counsel or our UH Office of Research Compliance

COMMON INSPECTION FINDINGS

- ⊗ **Failure to follow the investigational plan (protocol)**
    - ⊗ Investigation not conducted in accordance with the investigational plan
    - ⊗ Investigation not conducted in accordance with the signed statement of investigator
- ⊗ **Inadequate and/or inaccurate study records**
    - ⊗ Failure to prepare or maintain accurate case histories
- ⊗ **Inadequate study participant protection and Informed Consent issues**
    - ⊗ Failure to obtain informed consent in accordance with 21 CFR Part 50
- ⊗ **Inadequate accountability and/or control of the investigational product**
    - ⊗ Investigational drug disposition records not adequate
- ⊗ **Inadequate training of personnel on procedures and protocols**
- ⊗ **Failure to timely report and/or record protocol deviations and adverse events**
    - ⊗ Failure to report promptly to the IRB all unanticipated problems involving risk to subjects
    - ⊗ Failure to report AEs promptly to the sponsor
- ⊗ **Failure to implement a corrective action system to address identified issues and prevent recurrence**

WHERE TO GET HELP

- FDA Guidance for Industry - Investigator Responsibilities — Protecting the Rights, Safety, and Welfare of Study Subjects
- ICH E6(R3) - Guideline for Good Clinical Practice
- UH HRPP Investigator Manual
  - Chapter 5 - Research Staff Responsibilities
  - Chapter 24 - Clinical Trials Requirements
- Research Toolbox
  - Internal QA Checklist – Participant
  - Internal QA Checklist – Regulatory
  - ALCOA+C Documentation
- Research Standard Operating Procedures
  - QA-501 - FDA Inspections
  - SC-403 Research Documentation
  - SS-301 Maintenance of Research Regulatory Binders
  - GA-105 Investigator Responsibility for Study Team Training and Documentation
  - SC-405 Records Retention, Archive, and Storage

For additional assistance contact:

- Office of Research Compliance: uhresearchcompliance@uhhospitals.org
- The Clinical Research Center: ClinicalResearch@UHhospitals.org
- The UH IRB: uhirb@uhhospitals.org

REFERENCES

- Compliance Manual for Clinical Investigators and Sponsor-Investigators: https://www.fda.gov/media/75927/download